REMARKS

Reconsideration of the above-identified application, in view of the following remarks, is respectfully requested.

I. Certified Croatian Priority Document

On December 12, 2003 Applicants submitted a claim for priority based on Croatian Application No. P 20020614, filed July 22, 2002, along with a certified copy of the Croatian priority document. A copy of the postcard stamped by the USPTO acknowledging receipt of the priority document is attached hereto. The Examiner is requested to acknowledge receipt of the Croatian priority document with the next Office Action.

II. Status Of The Claims

Claims 1, 23, and 24 have been amended to correct minor typographical errors. The amendments to claims 1, 23, and 24 are not narrowing amendments. Claim 33 has been amended to more clearly define the nature of the substantially pure amorphous 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A recited therein, and to conform to proper U.S. practice. Support for this amendment can be found, for example, in the specification at page 35, lines 3-9 (Example 19). Amended claim 36 is directed to a method of treating bacterial and protozoal infections in humans and animals. New claim 37 is directed to a method of treating inflammation related diseases, as originally recited in claim 36.

New claims 37-41 have been added. Support for these new claims can be found, for example, in the specification at page 1, lines 25-28, page 6, lines 25 to page 7, line 9, and page 18, lines 22-28, and in original claim 36.

Claims 1-41 are pending in this application and are at issue.

III. Rejections Under 35 U.S.C. §112

Claim 36 has been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the specification, while being enabling for a method of treating bacterial or protozoal infections, does not reasonably provide enablement for the treatment of inflammation-related diseases. The Examiner concedes that azalide antibiotics are well known for the treatment of bacterial or protozoal infections, but asserts that since the use of these compounds is not well known for treating inflammation-related diseases, there is good reason to doubt that the claimed method is effective, in the absence of supporting evidence to this effect in the specification.

Claim 36 has been amended to delete the phrase "and inflammation related diseases", which is the subject of new claim 37. Applicants believe that the rejection of claim 36 is moot, and respectfully request that it be withdrawn.

With respect to any future rejection of claims 37 and 41 for lack of enablement, Applicants present the following remarks:

Contrary to the Examiner's assertion, the anti-inflammatory effects of macrolide antibiotics were known at the time the present invention was made. The Examiner's attention is directed to Čulić *et al.*, *Eur. J. Pharmacol.*, 429 (2001), pp. 209-229 (Exhibit 2). As can be seen from the Abstract on page 209, although macrolides are widely used as antibacterial drugs, "[c]lincal and experimental data, however, indicate that they also modulate inflammatory responses, . . . opening new opportunities for the therapy of other inflammatory conditions." See also section 7 of Exhibit 2, at pages 220-223.

Azithromycin differs from other macrolide antibacterials in that it exhibits unusual pharmacokinetic properties. It is rapidly accumulated by cells and tissues, particularly by blood leukocytes, and is only slowly released from these sites. Čulić et al., *Eur. J. Pharmacol.*, 450

(2002), pp. 277-289 (Exhibit 3) discloses the results of a study of the effect on human neutrophils and circulating inflammatory mediators, performed using a standard antibacterial dose of azithromycin (500 mg/day p.o.) for 3 days. The results presented therein demonstrate that administration of azithromycin results in acute stimulation of neutrophil degranulation and phagocytosis-associated oxidative burst, together with a slight increase in serum interleukin-1β, which may contribute to the antibacterial activity of azithromycin, while acute down regulating effects on serum interleukin-8, growth related oncogene-α and soluble vascular cell-adhesion molecule-1, indicates potential anti-inflammatory actions of azithromycin. See Exhibit 3, page 287, right hand column.

The Examiner's attention is also directed to International Publication No. WO 02/087596 (filed April 10, 2002 and published on November 7, 2002, Exhibit 1), which relates to the use of azithromycin for the therapy of neutrophil-dominated non-infective inflammatory diseases.

Accordingly, in view of the recognition in the prior art that azithromycin and other macrolides may be utilized in the treatment of inflammation-related diseases, applicants believe that claims 37 and 41 are fully enabled.

Claim 36 has been rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. The Examiner contends that it is not clear whether the bacterial and protozoal infections and inflammation-related diseases are treated at the same time or separately.

Claim 36 has been amended to delete the phrase "and inflammation related diseases", which is the subject of new claim 37. This rejection is therefore moot, and should be withdrawn.

IV. Rejection Under 35 U.S.C. §102/103

Claims 1-39 have been rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Karimian *et al.* (U.S. Patent No. 6,245,903, "Karimian"). The Examiner contends that Karimian discloses a method for obtaining amorphous azithromycin in pure form by dissolving azithromycin in an organic solvent, followed by evaporating the solvent. See Karimian at col. 2, lines 53-57. The Examiner further asserts that even if there are any differences between Karimian and the claimed products and processes, they are minor in nature and thus the claims are *prima facie* obvious over the cited reference.

The rejection is respectfully traversed.

Claims 1-28 of the present application are directed to a process for preparing substantially pure amorphous azithromycin that requires the steps of (b) crystallizing an orthorhombic isostructural pseudopolymorph of azithromycin of formula (I), (c) isolating the orthorhombic pseudopolymorph, and (d) converting the orthorhombic pseudopolymorph to substantially pure amorphous azithromycin. Claims 29-31 are directed to the orthorhombic isostructural pseudopolymorph of Formula (I). Claims 32-36 are directed to substantially pure amorphous azithromycin prepared by the process of claim 1, and to compositions and methods of treatment using substantially pure amorphous azithromycin prepared by the process of claim 1.

Karimian is completely silent with respect to the formation and isolation of a crystalline orthorhombic isostructural pseudopolymorph of azithromycin, and is also silent regarding the use of orthorhombic pseudopolymorphs as intermediates in the preparation of substantially pure amorphous azithromycin.

Indeed, Karimian states, at col. 1, lines 51-57, that amorphous azithromycin cannot be made pure on a commercial scale, and that it can only be made in a pure form on a laboratory scale, by using a chromatographic purification step, or by starting with pure crystalline

azithromycin mono- or dihydrate. Moreover, Karimian further states that anhydrous azithromycin is unsuitable for formulations (see col. 2, lines 36-37).

At col. 1, line 49, Karimian teaches that the amorphous azithromycin prepared by the process of Example 1 of Canadian Patent No. 1 191 843 is a foam. In contrast, as evidenced by Figure 7, page 8, lines 1-2, and page 17, lines 25-30 of the specification, the substantially pure amorphous azithromycin of the present invention is a free-flowing granular product.

Indeed, the substantially pure amorphous azithromycin of the present invention has superior and unexpected properties when compared to either commercial azithromycin dihydrate or the amorphous azithromycin described by Karimian.

As can be seen at pages 34 and 35 of the specification, and with reference to Table 2 and Figures 8, and 9, the substantially pure amorphous azithromycin of the present invention (prepared according to Example 11) has a significantly improved specific dissolution rate (see Figures 8 and 9) compared to azithromycin dihydrate, and also has a significantly higher intrinsic dissolution rate (IDR) of about 2.79 mg min^{-1} cm^{-2} (at pH 6 and 37°C) when compared to that of azithromycin dihydrate (IDR of about 1.8 mg min^{-1} cm^{-2} at pH 6 and 37°C). See Example 19.

Moreover, the intrinsic dissolution rate of the substantially pure amorphous azithromycin of the present invention (prepared according to Example 11) is approximately 11% greater than that of the amorphous azithromycin described by Karimian (i.e., amorphous azithromycin prepared according to Example 1 of Canadian Patent No. 1 191 843, which has an IDR of about 2.50 mg min^{-1} cm^{-2} at pH 6 and 37°C). Indeed, the dissolution of the substantially pure amorphous azithromycin of the present invention (prepared according to Example 11) is approximately 30% greater after 60 minutes (at pH 3 and 37°C) than that of the amorphous azithromycin prepared according to Example 1 of Canadian Patent No. 1 191 843.

The preceding evidence will be confirmed by a comparative showing under 37 C.F.R. § 1.132 if desired by the Examiner.

Because Karimian does not teach or suggest the substantially pure amorphous azithromycin of the present invention, the orthorhombic isostructural pseudopolymorphs of azithromycin of Formula (I), or a process that involves (i) crystallizing an orthorhombic isostructural pseudopolymorph of azithromycin of formula (I), (ii) isolating the orthorhombic pseudopolymorph, and (iii) converting the orthorhombic pseudopolymorph to substantially pure amorphous azithromycin (as required by steps (b) - (d) of claim 1), it does not anticipate or render obvious any of the present claims.

In view of the above amendments and remarks, applicants believe that each of the pending claims in this application is in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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